

Sugar-based Crown Ethers in Enantioselective Syntheses

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Abstract

A number of chiral macrocyclic compounds have been prepared that contain a monosaccharide-derived sub-unit. These sugar-based crown ethers were used as chiral phase transfer catalysts in a few asymmetric reactions. A few of them proved to be effective catalysts in Michael additions, a Darzens condensation and an epoxidation of α,β -enones. It was found that the type of the monosaccharide, the substituents on the sugar unit and on the nitrogen atom of the macroring have a significant influence on both the yield and the enantioselectivity.

Keywords

chiral crown ethers, phase transfer catalysis, asymmetric reactions

1 Introduction

The synthesis and investigation of sugar-based crown ethers was an interesting and up to date topic in the last decades at our department. The basis of our research is the finding that the chiral crown ethers incorporating monosaccharide moiety in their ring, are able to generate asymmetric induction as chiral phase transfer (PT) catalysts in certain reactions. Phase transfer catalysis has been recognized as a versatile methodology for organic synthesis, based on its simple experimental operations, mild reaction conditions using inexpensive and environmentally benign reagents and solvents (very often water). A few of chiral PT catalysts have been successfully used in asymmetric reactions. Chiral phase transfer catalysis has become an attractive area in the „green” chemical discipline, and many types of chiral catalysts have been developed and applied over the past few decades [1-3].

Crown ethers with carbohydrate moieties form a special group of the chiral PT catalysts. Sugars are suitable source of chirality and their basic chemistry is well explored. They are available in enantiomerically pure form with known chiroptical properties. Carbohydrates are unusually well-endowed with functionality which can be used to build in secondary binding sites, as well as catalytic sites. A part of the starting monosaccharides is easily available commercial product. Crown ethers containing a sugar unit incorporated in the macrocyclic ring may be built from various monosaccharides; thus macrocycles of different chirality are available [4-5].

2 Results and discussion

We have synthesized a variety of chiral crown ethers containing one sugar unit in annelation with the macrocyclic ring from various monosaccharides such as D-glucose, D-mannose, D-galactose, D-altrose, 2-deoxy-D-ribo-hexopyranoside, L-arabinose and from sugar alcohols as L-treitol, D-mannitol. These macrocycles differed significantly from each other by the chirality of the sugar units, the size of macrocyclic ring and the number and sort of the heteroatoms in the crown ring. The most important types of the sugar-based crown ethers developed by us can be seen in Fig. 1.

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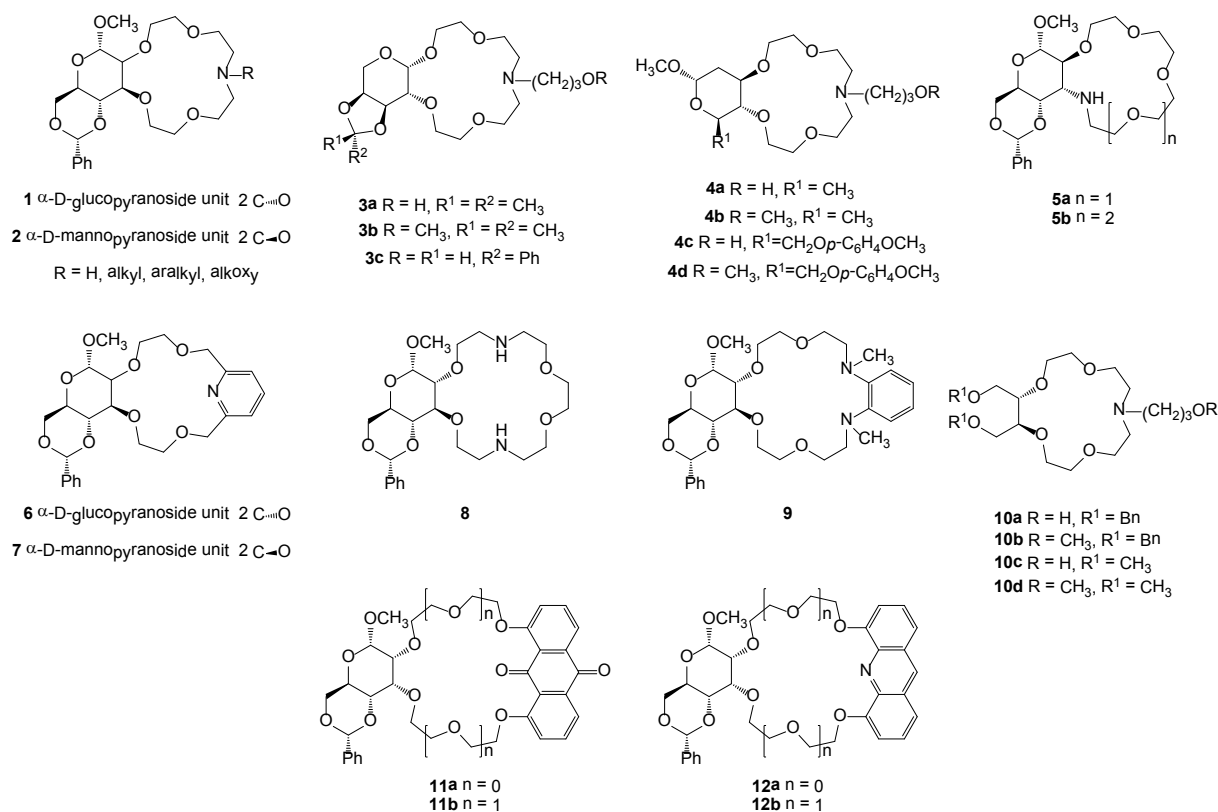


Fig. 1 Monosaccharide-based chiral crown ethers

Monoaza-15-crown-5 type macrocycles annelated to protected monosaccharides with different side arms (with heteroatoms at the end) on the nitrogen atom of the crown ring, were synthesized in many steps (**1-4**, **10**). This type of macrocycles named lariat (lasso) ethers or armed crown ethers having heteroatom containing podand arms are suitable to be involved in encapsulated complexation and display high lipophilic character and unique guest specificity due to the macroring - side arm cooperativity [6-7].

The synthesis of methyl- α -D-glucopyranoside- and methyl- α -D-mannopyranoside-based lariat ethers (**1**, **2**) [8], crown ethers consisting L-arabinose units (**3**) [9], 2-deoxy-*ribo*-hexopyranoside- and altrose-based macrocycles (**4**, **5**) [10] and D-glucose- and D-mannose-based monoaza-15-crown-5 compounds with pyridine-ring (**6**, **7**) [11] were published by us in the last years. In addition, diaza crown ethers having 15- and 18-membered ring which contained secondary and tertiary amino groups (**8**, **9**), monoaza-15-crown-5 type compounds with L-treitol units (**10**), and glucopyranoside-based macrocycles containing 9,10-anthraquinone or acridine fluorescent signalling units (**11**, **12**), have also been synthesized [12].

In all cases, first a protected monosaccharide derivative with two free vicinal hydroxyl groups was prepared, then the crown ring was built up on the hydroxyl groups of the compound. The preparation of lariat ethers is shown via the example of the 2-deoxy-*ribo*-hexopyranoside-based macrocycles (**4**) (Fig. 2) [10].

The synthesis of one of the key compounds (**16**) involves the opening of the benzylidene acetal ring of 2,3-anhydro derivative **13** that was performed with *N*-bromosuccinimide (NBS). The benzoyl group of the intermediate was removed by reaction with sodium methylate in methanol to provide bromo sugar **14**. The bromo function of intermediate **14** was removed by hydrogenolysis in the presence of Pd/C to give species **15**. The regioselective reductive ring opening was accomplished by LiAlH₄ in THF to afford methyl 2,6-dideoxy- α -D-*ribo*-hexopyranoside (**16**).

Another key compound (**19**) was prepared by the reductive ring opening of 2,3-anhydro derivative **13** carried out with tetrabutylammonium tetrahydroborate (Bu₄NBH₄) leading to the diaxial ring opening product, methyl 4,6-*O*-benzylidene-2-deoxy- α -D-*ribo*-hexopyranoside (**17**). Removal of the benzylidene acetal moiety in compound **17** was performed by catalytic hydrogenation to furnish methyl-2-deoxy- α -D-*ribo*-hexopyranoside (**18**). Selective protection of the C-6 hydroxyl group was achieved by the Mitsunobu reaction using 4-methoxyphenol, diisopropyl-azodicarboxylate and triphenyl phosphine (**19**). The vicinal hydroxyl groups of compounds **16** and **19** were alkylated with bis(2-chloroethyl) ether in the presence of tetrabutylammonium hydrogensulfate (Bu₄HSO₄) as the catalyst and 50 % *aq.* NaOH as the base in a liquid-liquid two-phase system to give intermediates **20** and **21** in 45 % and 52 % yields, respectively, after chromatography. The exchange of chlorine to iodine in intermediates **20** and **21** was accomplished by reaction with NaI in boiling acetone to afford bis-iodo derivatives

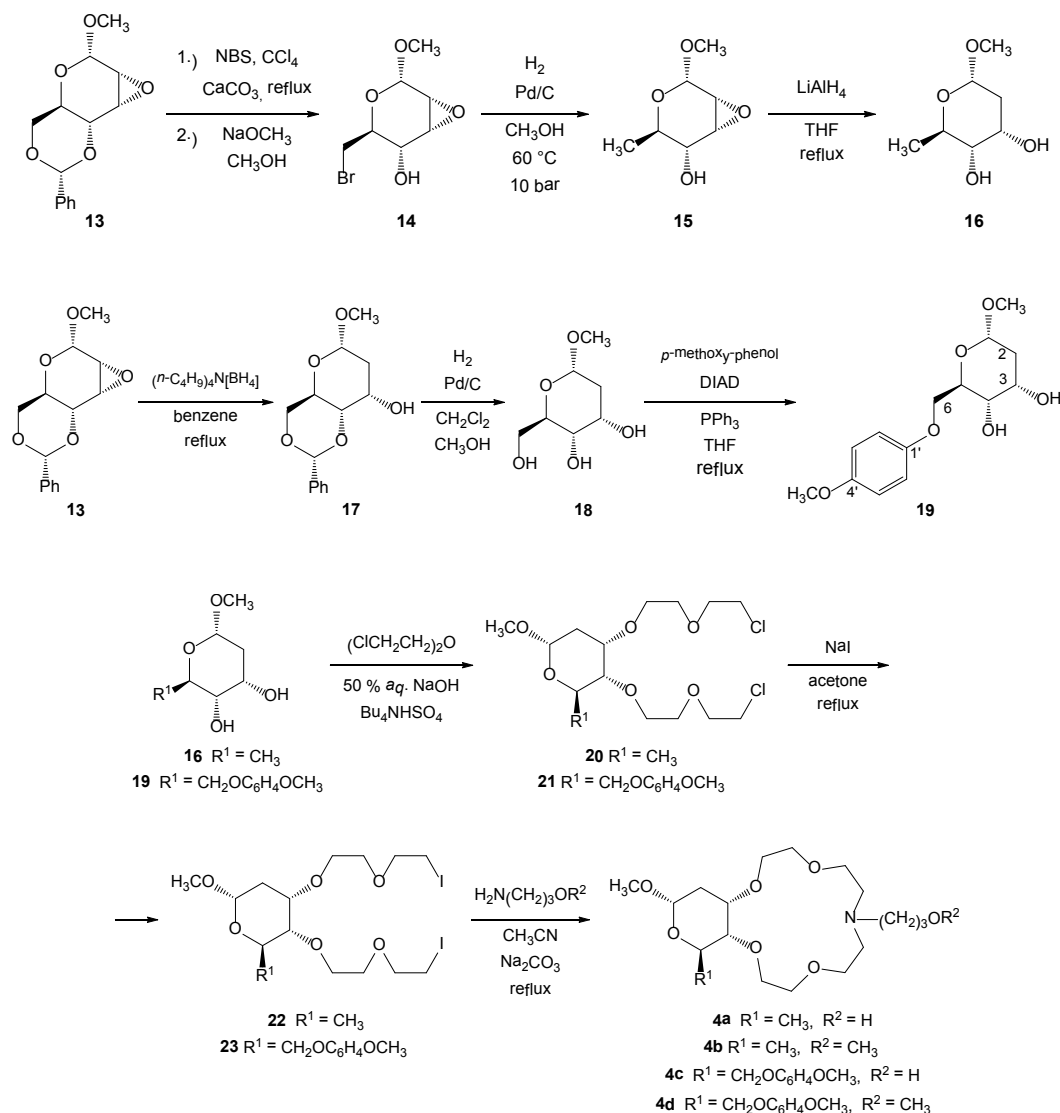


Fig. 2 Preparation of 2-deoxy-ribo-hexopyranoside-based lariat ethers **4a-d**

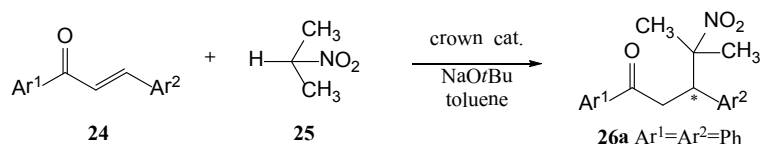


Fig. 3 Asymmetric addition of 2-nitropropane (**25**) to α,β -enones (**24**)

22 and **23**, respectively. These compounds were then cyclized with two kinds of primary amines, such as 3-aminopropanol and 3-methoxypropylamine, in boiling acetonitrile, in the presence of dry Na_2CO_3 to furnish azacrown ethers **4a-b** and **4c-d**, respectively. It is interesting to note that the yields of 2,6-dideoxy-ribo-hexopyranoside-based lariat ethers (**4a** and **4b**) were relatively low (46 % and 30 %, respectively), while those of the macrocycles having *p*-methoxyphenyl substituent (**4c** and **4d**) were much higher (79 % and 84 %, respectively) [10].

2.1 Enantioselective reactions

The sugar-based crown ethers were used as chiral phase transfer catalysts in a few asymmetric reactions. A few of them proved

to be efficient catalyst in two Michael additions, in a Darzens condensation and in the epoxidation of α,β -enones. It was found that the type of the monosaccharide, the substituents on the sugar unit and on the nitrogen atom of the macrocyclic have had a significant influence on both the yield and the enantioselectivity [5].

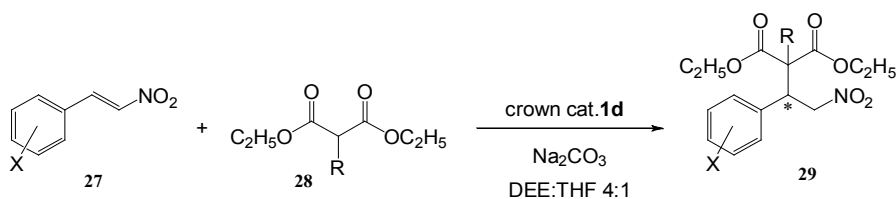
The two Michael additions used as model reactions were performed in solid-liquid phase at room temperature. The addition of 2-nitropropane (**25**) to α,β -enones (**24**) was carried out in dry toluene, in the presence of solid sodium *tert*-butoxide (35 mol%) and one of the chiral catalysts (7 mol%). (Fig. 3) [5, 8-9, 11, 13].

Choosing chalcone (**24a**, $\text{Ar}^1=\text{Ar}^2=\text{Ph}$) as the starting material, the relationship between the structure of the catalyst and its

Table 1 Effect of the side arms of the catalyst in the reaction of 2-nitropropane and chalcone

Entry	Catalyst	R group of the catalyst	Time (h)	Yield of 26a (%) ^a	ee (%) ^b
1	1a	<i>n</i> -C ₄ H ₉	40	41	48
2	1b	CH ₂ C ₆ H ₅	22	39	46
3	1c	(CH ₂) ₂ OH	20	51	63
4	1d	(CH ₂) ₃ OH	28	53	87
5	1e	(CH ₂) ₃ OCH ₃	40	52	90
6	1f	(CH ₂) ₄ P(O)(OC ₂ H ₅) ₂	48	39	83
7	1g	(CH ₂) ₂ P(O)(C ₆ H ₅) ₂	12	41	74
8	1h	(CH ₂) ₃ P(O)(C ₆ H ₅) ₂	14	32	77
9	1i	(CH ₂) ₄ P(O)(C ₆ H ₅) ₂	10	43	95

^aBased on isolation by preparative TLC; ^bEnantioselectivities were determined by ¹H NMR spectroscopy in the presence of Eu(hfc)₃ as a chiral shift reagent; the (+)-*R*-antipode of the Michael adduct **26** was formed

**Fig. 4** Asymmetric addition of diethylmalonates (**28**) to β -nitrostyrenes

effect was studied. The L-arabinose-based lariat ethers (**4**) generated 61–64 % enantiomeric excess (ee) in this reaction [9]. The D-glucopyranoside-(**6**) and D-mannopyranoside-(**7**) based macrocycles incorporating a pyridine-ring induced ee values of 72 % and 67 %, respectively [11]. Using crown ethers comprising an α -D-glucopyranoside unit (**1**), formation of the (+)-*R* enantiomer was preferred, while applying α -D-mannose-based catalysts (**2**), the (–)-*S* enantiomer was in excess. The monoaza-15-crown-5 type lariat ethers annelated to the methyl 4,6-*O*-benzylidene- α -D-glucopyranoside unit (**1**) proved to be the most efficient catalysts. The effect of different *N*-substituents (R) could be observed from the results of the reaction carried out in the presence of lariat ether **1**. A few experiments selected are shown in Table 1. The enantioselectivities were better with the catalysts having hydroxyl/methoxy group (entries 3–5) or a *P*-function (entries 6–9) at the end of the side arm, as compared to the cases with alkyl and arylalkyl groups at the end (entries 1–2). The best result (95 % ee) was obtained with the catalyst containing a Ph₂P(O)(CH₂)₄ substituent (**1i**). The chain length of substituents is of crucial importance. There is an optimum length for the hydrocarbon spacer connecting the MeO or Ph₂P(O) moiety to the nitrogen atom of the azacrown ring. Among the catalysts tested, lariat ether **1e** with a three carbon atom spacer [(CH₂)₃-OCH₃] and macrocycle **1i** with a four carbon atom chain [(CH₂)₄-P(O)Ph₂] proved to be the best (90 % ee and 95 % ee, respectively) [5].

The asymmetric induction depends strongly on the nature of the Ar¹ and Ar² substituents of the α,β -enone as well. In the presence of **1d** [R=(CH₂)₃OH], the substituents in the aromatic ring of the chalcone (CH₃, OCH₃, NO₂, Cl, F) resulted in a decrease in the optical yield (14–68 % ee), as compared to

the case with the unsubstituted chalcone **26a** (87 % ee). From among the α,β -enones analogue to chalcone, the 1-naphthyl derivative (Ar¹=1-naphthyl-, Ar²=Ph) and *trans*-crotonophenone derivative (Ar¹=Ph, Ar²=Me) were formed with the highest ee value (87 % and 76 %, respectively) [5, 13].

Another Michael reaction, the conjugate addition of substituted diethylmalonates **28** to β -nitrostyrenes **27** was carried out in a (1:4) mixture of THF-ether as the solvent in the presence of dry Na₂CO₃ (used in two-fold excess) employing 15 mol% of the crown ether (Fig. 4). The (–)-(*S*) enantiomer of compound **29** was formed in the presence of catalyst **1d** [14–15].

It was found that the α -substituents of diethylmalonate influenced the extent of asymmetric induction. The results on the addition of a few α -substituted diethyl malonate to β -nitrostyrene were summarized in Table 2 (Entries 1–5).

As compared to the unsubstituted product **29a**, the substituted derivatives were formed in higher ee values. The methyl-, butyl-, OAc and NHAc derivatives (**29b**, **29c**, **29d** and **29e**) were obtained in ee values of 42 %, 22 %, 29 % and 99 %, respectively. The ee value of 99 % detected in the reaction of acetamidomaltonate is indeed considerable and refers to the role of the NH group in the asymmetric induction. It was found that the substituents of nitrostyrene also influenced the enantioselectivity. The results of the reaction of a few chloro-nitrostyrenes and nitro-substituted derivatives are shown in Table 2 (entries 6–9). It can be seen that the 4-chloro and the 4-nitro substituted products (**29h** and **29i**) were obtained in the highest (97–99 %) ee, in a yield of 65 % and 78 %, respectively [15].

The Darzens condensation taking place between aromatic α -chloro-carbonyl compounds (**30**) and aromatic aldehydes

Table 2 Addition of diethylmalonates **28** to β -nitrostyrenes **27** in the presence of catalyst **1d**

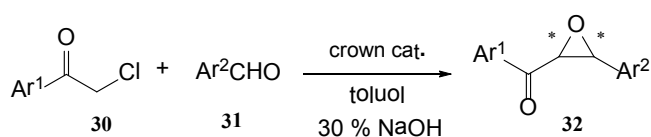
Entry	Product	R	X	Time (h)	Yield of 29 (%) ^a	ee (%) ^b
1	29a	H	H	20	61	20
2	29b	CH ₃	H	48	67	42
3	29c	<i>n</i> -C ₄ H ₉	H	100	50	22
4	29d	NHCOCH ₃	H	20	69	29
5	29e	NHCOCH ₃	H	3	60	99
6	29f	NHCOCH ₃	2-Cl	4	76	67
7	29g	NHCOCH ₃	3-Cl	4	61	72
8	29h	NHCOCH ₃	4-Cl	4	65	99
9	29i	NHCOCH ₃	4-O ₂ N	6	78	97

^a Based on isolation by preparative TLC; ^b Determined by chiral HPLC analysis, the (-)-(*S*) enantiomer was formed.

Table 3 Asymmetric Darzens condensations in the presence of catalyst **1d**

Entry	Ar ¹	Ar ²	Time (h)	Yield of 32 (%) ^a	ee (%) ^b
1	C ₆ H ₅	Ph	1	74	71
2	4-C ₆ H ₅ -C ₆ H ₄	Ph	1	54	96
3	4-C ₆ H ₅ -C ₆ H ₄	2-Cl-C ₆ H ₄	1	71	84
4	4-C ₆ H ₅ -C ₆ H ₄	4-H ₃ C-C ₆ H ₄	1	54	67
5	4-C ₆ H ₅ -C ₆ H ₄	2-Naphthyl	2	56	74
6	Furan-2-yl	2-Cl-C ₆ H ₄	5	77	70
7	Furan-2-yl	4-Cl-C ₆ H ₄	3	67	62
8	Thiophen-2-yl	Ph	5	63	71
9	Thiophen-2-yl	2-H ₃ C-C ₆ H ₄	3	79	68
10	Thiophen-2-yl	Piperonyl	5	57	86
11	Pyrrol-2-yl	1-Naphthyl	1	42	51

^a Based on isolation by preparative TLC; products **32** had a negative specific rotation; ^b Determined by ¹H NMR spectroscopy

**Fig. 5** Darzens condensation of aromatic α -chloro-carbonyl compounds and aldehydes

(**31**) was performed in toluene solution using 30 % NaOH at 22°C and took place in a stereoselective manner in the presence of chiral catalysts (Fig. 5). The *trans*-epoxyketone (**32**) was obtained in general in a diastereomeric excess (de) of >98 %, with a configuration of (-)-(*2R,3S*) [5, 8, 14, 16–18].

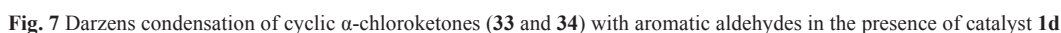
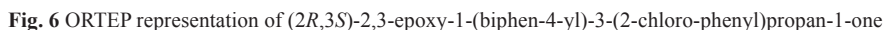
The aromatic unit (Ar¹) of the α -chloro-carbonyl compounds (**30**) were phenyl-, 2-furyl-, 2-thiophenyl-, 2-pyrrolyl. Benzaldehyde, substituted benzaldehydes, 1- and 2-naphthaldehydes and piperonal formed the choice of the aldehyde reactants. The use of D-glucose-based lariat ether **1d** (R=(CH₂)₃OH) as the catalyst gave the best results. The results of the reaction of a few aromatic aldehydes in the presence of the catalyst **1d** were summarized in Table 3 [14, 16].

The maximum selectivity (96 % ee) was detected in the reaction of 4-phenyl- α -chloroacetophenone with benzaldehyde (Table 3, entry 2). The substituents of benzaldehyde used as the

reactants had a significant impact on the yield and enantioselectivity (Table 3, entries 3–4 and 6–9) [17]. The α,β -epoxyketones with a furan (Table 3, entries 6–7) or a thiophene (Table 3, entries 8–10) moiety were obtained in good enantioselectivities (up to 86 % ee) as well as excellent diastereoselectivities (up to 98:2), but the epoxyketone with a pyrrole ring was formed in a low yield and enantioselectivity (Table 3, entry 11). The mannose-based crown ethers **2** generated lower enantioselectivities and promoted the formation of the enantiomer with a positive optical rotation [16].

The absolute configuration of a few epoxyketones was determined by single crystal X-ray analysis. As an example, we show the ORTEP representation of the epoxyketone obtained in the reaction of 4-phenyl- α -chloroacetophenone with 2-chlorobenzaldehyde. According to this, the absolute configuration is *2R,3S* (Fig. 6). It is reasonable to assume that the other epoxyketone derivatives with negative optical rotation also possess the same *2R,3S* absolute configuration [17].

The reaction of cyclic α -chloroketones with aromatic aldehydes was studied under the conditions described above in the presence of catalysts **1** and **2**. The reactions of 2-chloro-1-indanone (**33**) and 2-chloro-1-tetralone (**34**) with various aromatic aldehydes (**31**) were completed after a stirring of 20–40 minutes at 0°C in the presence of catalyst **1** (Fig. 7). The



It was found that the position of the substituents in the aromatic ring of the chalcone had a great impact on the yield and

Table 4 Effect of the *N*-side arms of the catalyst **1** in the epoxidation of chalcone (**24**, A¹=A²=Ph)

Entry	Catalyst	R	Time (h)	Yield of 32 (%) ^a	ee (%) ^b
1	1a	(CH ₂) ₂ OH	1	65	81
2	1b	(CH ₂) ₃ OH	1	82	94
3	1c	(CH ₂) ₃ OCH ₃	2	61	23
4	1d	(CH ₂) ₄ OH	1	65	41

^a Based on isolation by preparative TLC; ^b Enantioselectivities were determined by ¹H NMR spectroscopy; the (-)-(2*R*,3*S*)-antipode of the epoxyketone **32** was formed

Table 5 Asymmetric epoxidation of chalcone, substituted chalcones and chalcone analogues in the presence of the catalyst **1d**

Entry	Ar ¹	Ar ²	Time (h)	Yield of 32 (%) ^a	[α] _D ²² ^b	ee (%) ^c
1	Ph	Ph	1	82	-196	94
2	4-Cl-C ₆ H ₅	Ph	2	71	-182	97
3	4-H ₃ CO-C ₆ H ₅	Ph	3	58	-199	95
4	3-O ₂ N-C ₆ H ₅	Ph	1	55	-147	99
5	But	Ph	16	86	-239	90
6	1-Naphthyl	Ph	10	64	-188	67
7	2-Naphthyl	Ph	3	30	-138	87
8	But	1-Naphthyl	12	60	-48	85
9	But	2-Naphthyl	12	52	-253	92
10	N-Methyl-2-pyrrolyl	Ph	46	80	-210	79

^a Based on isolation by preparative TLC; ^b Enantioselectivities were determined by ¹H NMR spectroscopy; the (-)-(2*R*,3*S*)-antipode of the epoxyketone **32** was formed

enantioselectivity. The lowest enantioselectivities (62–83 % ee) were found in the case of the *ortho*-substituted model compounds, while the highest ee values (ee of 95–99 %) were obtained in the case of *para*-substituted models (good results of a few experiments in Table 5, entries 1–4). The epoxidation of the chalcone analogues are summarized in Table 5 (entries 5–10). The best enantiomeric excess values were obtained for the epoxyketone with R¹=But and R²=Ph, (90 % ee) or R¹=But and R²=2-naphthyl (92 % ee) [19].

Finally, two glucopyranoside-based crown ethers, with acridine fluorescent signalling units were synthesized, the 15-membered ligand **12a** and the 21-membered ligand **12b**. Their complexation properties toward alkali and alkali earth metal ions, and their enantioselectivity towards chiral ammonium salts were studied by absorption and fluorescence spectroscopic experiments. Macrocycle **12a** formed 1:1 complexes with all the metal ions selected and the stability constants were low (lg K < 2.3). The cavity-size of **12b** only afforded the complexation of organic ammonium ions. It showed chiral discrimination in case of all the four ammonium salts used as model guest compounds. The highest enantioselectivity (K(*R*)/K(*S*) ~ 3) was observed in case of the enantiomers of phenylethyl-ammonium (PEA) perchlorate. Ligand **12b** forms much more stable complexes with metal ions, the highest stability constant was obtained for the Ca²⁺ complex (lg K = 6.15). The coordination of metal ions by species **12b** was accompanied by a marked

fluorescence enhancement, whereas the binding of ammonium ions by the same ligand resulted in significant fluorescence quenching [12].

3 Summary

We have synthesized a variety of chiral crown ethers containing one sugar unit in annelation with the macrocyclic ring from various monosaccharides such as D-glucose, D-mannose, D-galactose, D-altrose, 2-deoxy-D-*ribo*-hexopyranoside, L-arabinose and from sugar alcohols as L-treitol, D-mannitol. A few representatives of the monosaccharide-based crown ethers induced a considerable asymmetric induction in certain reactions. On the basis of our experiences, it can be concluded that in the case of monoaza-15-crown-5 lariat ethers incorporation of a D-glucose moiety results in the most efficient catalysts. The glucose-based catalysts with (CH₂)₃OH substituent on the nitrogen atom (**1d**) showed the best results regarding the enantioselectivity. In the reaction of 2-nitropropane with chalcone and chalcone analogue α,β-enones 48–95 % ee values were measured. Addition of diethylmalonates to β-nitrostyrenes gave the Michael adducts in an enantioselectivity of 20–97 %. The epoxyketones were obtained in 51–96 % ee values in Darzens condensations and in 67–99 % ee values in epoxidation of α,β-enones in the presence of catalyst **1d**. The development of novel catalysts is of practical importance, as the lariat ethers can be utilized in a variety of phase transfer catalytic reactions, a part of which is to be explored.

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